

Dynamic Implicit-Solvent Coarse-Grained Models of Lipid Bilayer Membranes : Fluctuating Hydrodynamics Thermostat

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Abstract: Many coarse-grained models have been developed for equilibrium studies of lipid bilayer membranes. To achieve in simulations access to length-scales and time-scales difficult to attain in fully atomistic molecular dynamics, these coarse-grained models provide a reduced description of the molecular degrees of freedom and often remove entirely representation of the solvent degrees of freedom. In such implicit-solvent models the solvent contributions are treated through effective interaction terms within an effective potential for the free energy. For investigations of kinetics, Langevin dynamics is often used. However, for many dynamical processes within bilayers this approach is insufficient since it neglects important correlations and dynamical contributions that are missing as a result of the momentum transfer that would have occurred through the solvent. To address this issue, we introduce a new thermostat based on fluctuating hydrodynamics for dynamic simulations of implicit-solvent coarse-grained models. Our approach couples the coarse-grained degrees of freedom to a stochastic continuum field that accounts for both the solvent hydrodynamics and thermal fluctuations. We show our approach captures important correlations in the dynamics of lipid bilayers that are missing in simulations performed using conventional Langevin dynamics. For both planar bilayer sheets and bilayer vesicles, we investigate the diffusivity of lipids, spatial correlations, and lipid flow within the bilayer. The presented fluctuating hydrodynamics approach provides a promising way to extend implicit-solvent coarse-grained lipid models for use in studies of dynamical processes within bilayers.

I. INTRODUCTION

Many coarse-grained models have been developed for equilibrium studies of lipid bilayer membranes [9–14, 16–18, 20–23]. To achieve in simulations access to length-scales and time-scales difficult to attain in fully atomistic molecular dynamics, these coarse-grained lipid models have been developed to provide a reduced description of the molecular degrees of freedom and often remove entirely representation of the solvent degrees of freedom [11–13, 16, 18, 20, 22]. In such implicit-solvent models, the solvent contributions are treated through effective interaction terms within an effective potential for the free energy. Dynamical processes are then often investigated using Langevin dynamics [12, 13, 18, 20]. However, for many problems this approach is insufficient since it neglects important correlations and dynamic contributions from the momentum transfer that would have occurred through the solvent. To incorporate these effects, we introduce a thermostat based on fluctuating hydrodynamics for dynamic simulations of implicit-solvent coarse-grained models. Our approach couples the coarse-

grained degrees of freedom to a stochastic continuum field that accounts for both the solvent hydrodynamics and thermal fluctuations. We present a general mathematical framework and specific methods for how to couple these descriptions in a manner consistent with statistical mechanics and in a manner amenable to efficient computational methods [7, 8]. We then present a number of results for dynamical properties of the fluctuating hydrodynamics bilayer model. We present results for both self-assembled planar bilayers and self-assembled vesicles. In particular, we consider the relaxation of the mean-squared displacement characterizing diffusivity of lipids within the bilayer for both the fluctuating hydrodynamics method and conventional Langevin dynamics. We next consider the correlations between the motions of an individual lipid and those of its neighbors within a patch of varying size. Finally, we consider the pair correlations for the motions of lipids within the bilayer. We find interesting vortex-like flow structures for the correlated lipid motions within the bilayer that are similar to those observed in explicit solvent bilayer simulations. We expect the introduced fluctuating hydrodynamics methods to provide powerful new approaches for performing dynamical studies utilizing implicit-solvent coarse-grained models.

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II. IMPLICIT-SOLVENT COARSE-GRAINED LIPID MODEL

Many coarse-grained implicit-solvent models have been developed for equilibrium studies of lipid bilayer membranes [12–14, 16, 17, 20, 22, 23]. These models capture at different levels of resolution the molecular details of lipids. To demonstrate our approach, we shall focus on the specific coarse-grained lipid model developed by Cooke and Deserno [12, 13]. In this model each lipid is

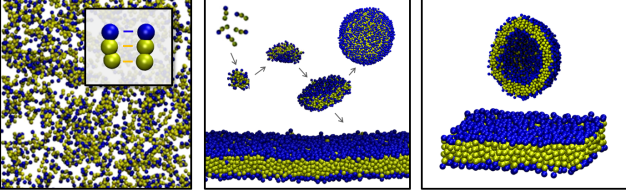


FIG. 1: Implicit-Solvent Coarse-Grained Lipid Model : Individual lipids are modeled by three coarse-grained units that interact to mimic amphiphilic molecules [12]. Starting from a concentrated solution of model lipids, structures are self-assembled (left). The self-assembly proceeds initially through the formation of aggregates that resemble micelles which subsequently merge into larger disk-like structures (middle). These structures merge further and after reaching a critical size they either orient to span the entire periodic domain as a planar bilayer or wrap spontaneously to form a vesicle (middle and right).

represented by three coarse-grained units. The first unit accounts for the polar hydrophilic head group of the lipid and the remaining two units account for the hydrophobic groups along the hydrocarbon tail of the lipid, see Figure 2. An effective interaction potential is developed that takes into account excluded volume interactions, van der Waal’s attraction, and the hydrophobic-hydrophilic effect. The solvent mediated effects that drive formation of the bilayer structure is taken into account through a long-range attractive interaction term between the tail units in the coarse-grained model. To obtain robust bilayers that exhibit a fluid phase, it was found important to use an attractive interaction that has a broad energy well [12].

Extensive studies have been performed to parameterize this lipid model to obtain reasonable equilibrium properties, such as the bilayer bending elasticity, compression modulus, average area per lipid, and tension [12]. Throughout, we shall use the specific parameterization given in Table I. An important feature of the lipid model is the self-assembly of stable bilayer structures from a solution of lipids. For our studies, we have performed simulations over long trajectories to self-assemble both planar bilayer sheets and vesicles, see Figure 2. For the planar bilayer case with periodic boundary conditions, special care must be taken to obtain an appropriate domain size

Parameter	Description	Value
σ	lipid radius	1.0 nm
ϵ	energy scale	2.5 kJ·M ⁻¹
m_0	reference mass	1 amu
w_c	energy potential width	1.2 σ
m	lipid mass	720 m_0
τ	time-scale	$\sigma\sqrt{m_0/\epsilon} = 0.6$ ps
$k_B T$	thermal energy	1.0 ϵ
ρ	solvent mass density	602 m_0/σ^3
μ	solvent viscosity	383 $m_0/\tau\sigma$
Υ	drag coefficient	7210 m_0/τ

TABLE I: Parameterization of the Fluctuating Hydrodynamics Lipid Model

to ensure a small surface tension of the constructed bilayer. We have implemented a modified Andersen thermostat/barostat to equilibrate our planar bilayers in the γNVT ensemble with zero surface tension $\gamma = 0$, see [1]. We use in our dynamic studies a fixed domain having the average of the sampled domain sizes. In the case of the vesicle bilayer, no such special thermostating was required. On a large domain, we simulated a concentrated solution of lipids over several distinct long trajectories. In a subset of these trials we obtained spontaneous self-assembly of vesicles, see Figure 2.

III. FLUCTUATING HYDRODYNAMICS THERMOSTAT

To account for the contributions of momentum transfer through the missing solvent degrees of freedom, we introduce a continuum stochastic field for the solvent that accounts for both hydrodynamics and thermal fluctuations. For this purpose, we introduce the following fluctuating hydrodynamic equations

$$\rho \frac{d\mathbf{u}}{dt} = \mu \Delta \mathbf{u} - \nabla p + \Lambda [\Upsilon (\mathbf{V} - \Gamma \mathbf{u})] + \mathbf{f}_{thm} \quad (1)$$

$$\nabla \cdot \mathbf{u} = 0 \quad (2)$$

$$m \frac{d\mathbf{V}}{dt} = -\Upsilon (\mathbf{V} - \Gamma \mathbf{u}) - \nabla \Phi + \mathbf{F}_{thm} \quad (3)$$

$$\frac{d\mathbf{X}}{dt} = \mathbf{V}. \quad (4)$$

The \mathbf{u} denotes the velocity of the solvent fluid and \mathbf{X}, \mathbf{V} denotes the collective positions and velocities of the coarse-grained particles. The p denotes the pressure that imposes the incompressibility of the solvent fluid, $\nabla \cdot \mathbf{u} = 0$. The ρ is the mass density of the solvent, μ is the shear viscosity, m is the mass matrix of the coarse-grained particles, and Φ is the potential energy of the coarse-grained particles. The thermal fluctuations are taken into account through the stochastic driving fields \mathbf{f}_{thm} and \mathbf{F}_{thm} . These are δ -correlated Gaussian random

fields with covariances

$$\langle \mathbf{f}_{thm}(s) \mathbf{f}_{thm}(t)^T \rangle = -2k_B T (\mu \Delta - \Lambda \Upsilon \Gamma) \delta(t - s) \quad (5)$$

$$\langle \mathbf{F}_{thm}(s) \mathbf{F}_{thm}(t)^T \rangle = 2k_B T \Upsilon \delta(t - s) \quad (6)$$

$$\langle \mathbf{f}_{thm}(s) \mathbf{F}_{thm}(t)^T \rangle = -2k_B T \Lambda \Upsilon \delta(t - s). \quad (7)$$

Through the operators Υ and Γ , the term $-\Upsilon(\mathbf{V} - \Gamma \mathbf{u})$ provides an effective coarse-grained model of how the local fluid flow exerts a drag force on the coarse-grained particles. The Λ operator then models for the drag force

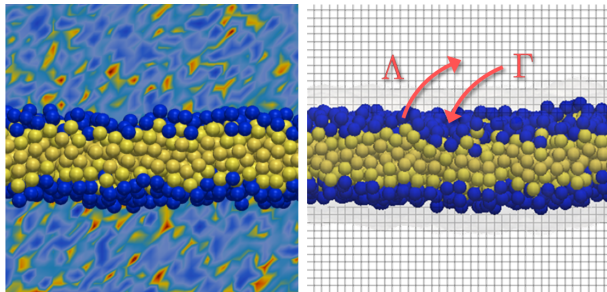


FIG. 2: Fluctuating Hydrodynamics Thermostat. The stochastic velocity field of the solvent fluid during the bilayer simulation (left). The Eulerian fluctuating hydrodynamic fields of the solvent are coupled to the Lagrangian degrees of freedom of the lipids through the operators Λ and Γ (right).

how the equal-and-opposite forces exerted on the solvent are spatially distributed within the fluid body. An important condition is that the coupling operators be adjoints $\Gamma = \Lambda^*$, see [7]. This adjoint condition ensures the dissipation occurs only through the Υ drag and not as a consequence of the interconversion operators Γ, Λ [7]. For the thermal fluctuations, the adjoint condition also greatly simplifies the form of the correlations of the stochastic driving fields and the algorithms needed for their computational generation [7]. We refer to the coarse-grained fluctuating hydrodynamics approach of equations 1–7 and related computational methods as the Stochastic Eulerian Lagrangian Method (SELM). The key feature of this approach is the mixed use of an off-lattice Lagrangian description of the lipids that is coupled to an on-lattice Eulerian description of the solvent fluid. This feature allows for leveraging numerical approaches from computational fluid dynamics and from molecular dynamics to perform efficient simulations of the coarse-grained fluctuating hydrodynamics model.

Throughout, we shall use the specific coupling operators

$$\Gamma \mathbf{u} = \int_{\Omega} \eta(\mathbf{y} - \mathbf{X}(t)) \mathbf{u}(\mathbf{y}, t) d\mathbf{y} \quad (8)$$

$$\Lambda \mathbf{F} = \eta(\mathbf{x} - \mathbf{X}(t)) \mathbf{F}. \quad (9)$$

While other choices are possible and may be desirable, this approach is based on the Stochastic Immersed Boundary Method [8]. We use the kernel functions $\eta(\mathbf{z})$

chosen to be the Peskin δ -Function given in [19]. This choice is made instead of the Dirac δ -Function to ensure a model in which the mobility of individual particles have a finite effective hydrodynamic radius within the fluid [8]. This choice also has important numerical properties that ensure to a good approximation translational invariance of the coupling despite the breaking of this symmetry by the discretization lattice of the fluid [8, 19]. While other choices of the coupling operators are possible, the Stochastic Immersed Boundary Method has been shown to provide a computationally efficient method for obtaining correct far-field hydrodynamic correlations and has a well-characterized near-field interaction [4–6, 8].

IV. COMPARISON WITH LANGEVIN DYNAMICS

The SELM fluctuating hydrodynamics thermostat is compared to the conventional Langevin dynamics by considering two cases. In the Langevin dynamics, we consider the case when the drag coefficient is comparable to the Stokes drag of a particle of size σ immersed in water, $\Upsilon = 7210 m_0/\tau$. We also consider the case corresponding to many Langevin simulations in the literature where the drag coefficient is taken artificially small to achieve efficient equilibration and sampling, $\Upsilon = 0.06 m_0/\tau$ [12, 13]. For the reference Lennard-Jones units σ, ϵ, m_0 , see Table I. We remark that for the small drag case the dynamics are in an inertial regime exhibiting a coherent velocity on the time-scale for collisions to occur between the lipids. In this regime, the collisions are expected to result in significant momentum transfer between the lipids before the momentum is suppressed by the Langevin drag. These two cases provide a useful baseline for comparison to the momentum conserving SELM thermostat. Throughout the SELM simulations, we use the solvent-lipid coupling strength determined by the Stokes drag in water, $\Upsilon = 7210 m_0/\tau$.

A. Lipid Diffusivity within Planar Bilayers and Vesicles

We initially study the diffusivity of lipids within the bilayer using the conventional Langevin dynamics and then make a comparison with the SELM dynamics. The diffusivity considered is $D(t) = \langle \mathbf{X}^2(t) \rangle / t$ and non-dimensionalized by the small drag Langevin diffusivity $D_*(0)$ and time-scale $t_* = \sigma^2 / D_*(0)$. We perform studies of the diffusivity for both a planar bilayer and a vesicle. We find in both cases that the SELM fluctuating hydrodynamics thermostat exhibits marked differences with the Langevin dynamics, see Figure 3 and 4. In the case of the Langevin dynamics with Stokes drag, we see that while the SELM dynamics yields a comparable diffusivity, the relaxation to the steady-state occurs over a significantly longer time-scale. This is consistent with

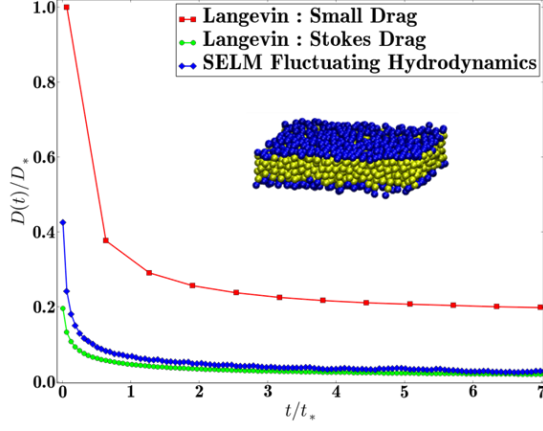


FIG. 3: Lipid Diffusivity within a Planar Bilayer.

the broad spectrum of time-scales associated with the relaxation of the individual hydrodynamic modes. For the

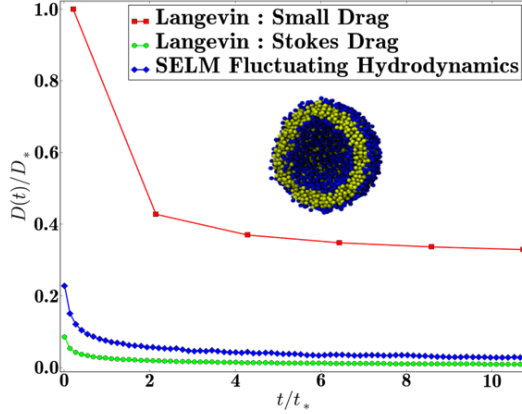


FIG. 4: Lipid Diffusivity within a Vesicle Bilayer.

fluctuating hydrodynamics thermostat, the well-known $t^{-3/2}$ decay of the velocity autocorrelation function can be established analytically in some limiting regimes and has been demonstrated in simulations [5]. As expected, compared to the Langevin dynamics with small drag, there is a significant reduction in the diffusivity under the SELM dynamics. However, compared to the Langevin dynamics with the Stokes drag coefficient, we find that the SELM dynamics yields lipids with a somewhat larger diffusivity. In this regime, we expect the diffusivity to be a consequence of the dissipation associated with the collective internal rearrangement modes of the lipids within the bilayer. We think the larger diffusivity under the SELM dynamics can be explained by two related mechanisms. The first is the local conservation of momentum that transmits momentum between lipids inducing local correlations and flows. The second is that the drag force acting on lipids depends only on the relative difference in velocity between the hydrodynamic field and the lipids.

This allows for rearrangements that are less dissipative when there is a coordinated deformation in the modes of the bilayer and fluid body. This is in contrast to the Langevin dynamics where momentum is ceded to an undeformable fixed ambient medium. Interestingly, as we shall discuss in latter sections, this result is somewhat in opposition to the alternative intuition that the obtained diffusivity under SELM dynamics might be smaller than the Langevin Stokes case as a consequence of the hydrodynamics giving additional local correlations. The hydrodynamics is expected to result in coupling of nearby lipids giving a type of coherent motion over a patch of the bilayer [2].

B. Correlations between Lipids within a Bilayer Patch

To characterize the correlations between lipids and those of its surrounding neighborhood, we consider the motion of an individual lipid and a patch. In particular, we consider for the displacement $\Delta_0 X$ of a given reference lipid over a time δt and its correlation to the displacement $\Delta_M X$ of the center-of-mass of a patch consisting of the M nearest neighbors. We consider the specific correlation $\langle \Delta_0 X \Delta_M X \rangle / \langle \Delta_0 X^2 \rangle$. The results for the SELM fluctuating hydrodynamics and Langevin dynamics are shown in Figure 5. For lipids that diffuse with

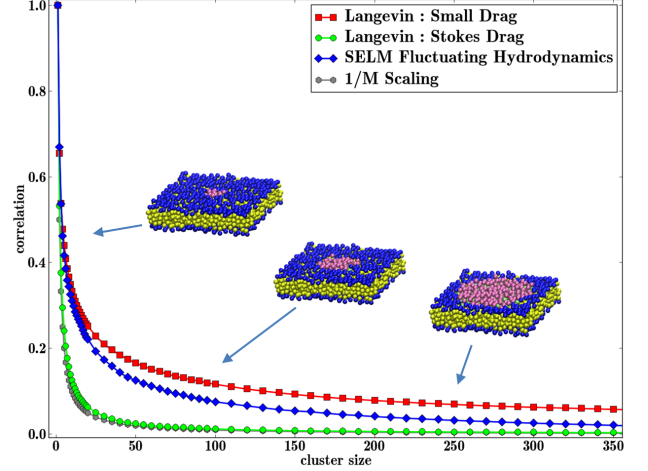


FIG. 5: Correlations between Lipids within a Bilayer Patch

only short-ranged correlations with their neighbors we expect a base-line correlation as the patch size grows to scale like $\sim 1/M$. The Langevin dynamics with small drag exhibits significant long-range correlations. In this case, the lipid dynamics exhibit significant inertial effects and momentum is transferred through collisions. This results in correlations between nearby lipids that are longer-ranged. In contrast, the Langevin dynamics having the Stokes drag coefficient exhibits the $1/M$ scal-

ing to a good approximation. This indicates that correlations in the displacements of the lipids within the bilayer are strongly suppressed by the Langevin drag. For the SELM dynamics using the same Stokes drag coefficient, we find long-range correlations persist between the lipids within the bilayer. This is a consequence of the important property that momentum is conserved for the SELM dynamics and that momentum can be transferred between lipids through the hydrodynamic fields. This is in contrast to the Langevin dynamics where momentum is simply ceded locally to a fixed ambient medium. As a consequence of the conservation of momentum in the SELM dynamics, the drag is expected to result in locally induced hydrodynamic flows. To characterize more precisely this behavior, we consider the pair correlation tensor for the motion of two lipids diffusing within the bilayer.

C. Spatial Correlations between Lipids within a Vesicle Bilayer

To characterize more precisely the spatial correlations between the motions of lipids diffusing within the bilayer, we consider the pair correlation tensor defined by $\Psi(\mathbf{r}) = \langle \Delta \mathbf{r} X \Delta_0 X^T \rangle$. In this notation, the displacements ΔX are taken over the time δt and the subscript specifies the displacement vector from the center-of-mass of a reference lipid to the center-of-mass of a second lipid within the bilayer, see Figure 6. The vector field

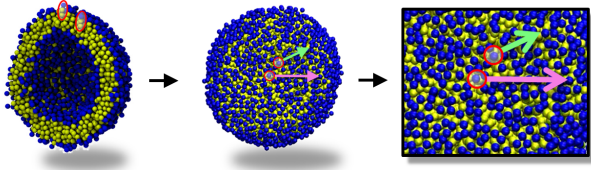


FIG. 6: Analysis of Spatial Correlations between Lipids within a Vesicle Bilayer

$\mathbf{w} = \Psi \mathbf{e}_1$ provides a characterization of the correlations in the flow of lipids within the bilayer. These spatial correlations are shown for the two types of Langevin dynamics considered and the SELM dynamics, see Figure 7. We find that for the Langevin dynamics with small drag coefficient, there is a significant lipid flow structure exhibited within the bilayer, see left of Figure 7 and 8. This appears to be a consequence of the interial dynamics and collision events that occur to transfer momentum laterally within the bilayer. In contrast, the Langevin dynamics with Stokes drag greatly suppresses this momentum transfer between lipids and there are no discernible spatial correlations, see middle of Figure 7 and 9. In the SELM dynamics with Stokes drag, interesting lipid flows are exhibited having a vortex-like structure, see right of Figure 7 and 10. In fact, very similar vortex-like flow structures have been observed in explicitly solvated sim-

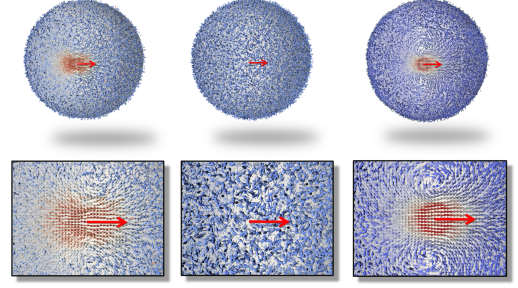


FIG. 7: Spatial Correlations between Lipids within a Vesicle Bilayer. Shown are results for Langevin with small drag $\Upsilon = 0.06 m_0/\tau$ (left), Langevin with Stokes drag $\Upsilon = 7210 m_0/\tau$ (middle), and SELM Fluctuating Hydrodynamics with $\Upsilon = 7210 m_0/\tau$ (right). For the Langevin dynamics with small drag and the SELM Fluctuating Hydrodynamics, lipid flows are observed exhibiting correlations resembling vortex-like structures.

ulations of lipid bilayers, see [2, 15]. Interestingly, similar lipid flows and spatial correlations have been offered as an explanation for recent neutron scattering experiments [3]. These results indicate that to obtain realistic lipid dynamics within bilayers it is important to conserve momentum and to incorporate the solvent mediated momentum transfer between lipids.

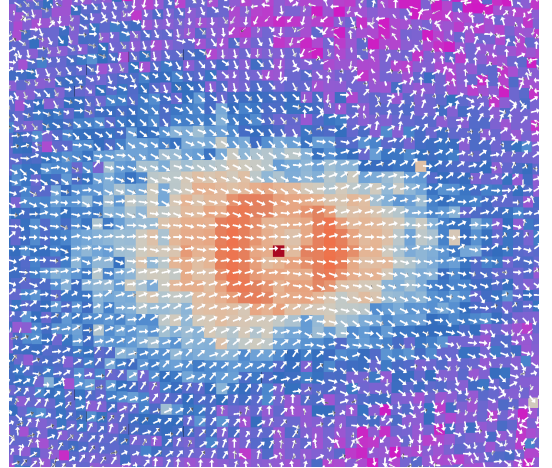


FIG. 8: Lipid Flow Correlations for Langevin with Small Drag $\Upsilon = 0.06 m_0/\tau$.

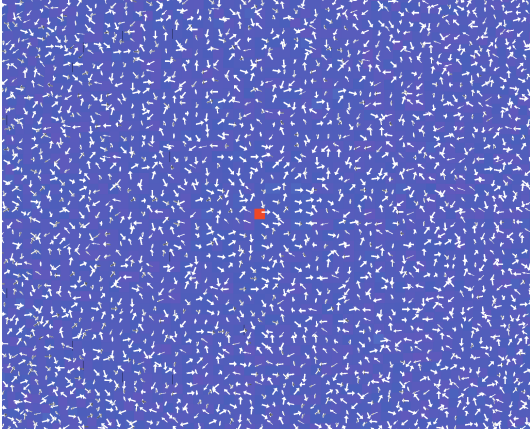


FIG. 9: Lipid Flow Correlations for Langevin with Stokes Drag $\Upsilon = 7210 \, m_0/\tau$.

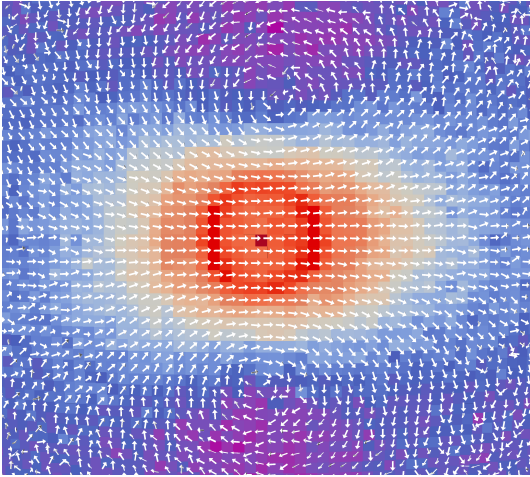


FIG. 10: Lipid Flow Correlations for SELM Fluctuating Hydrodynamics $\Upsilon = 7210 \, m_0/\tau$.

V. CONCLUSION

We have introduced a fluctuating hydrodynamics approach for dynamical studies of implicit-solvent coarse-grained lipid models. We have presented a general framework and specific methods for how to couple coarse-grained degrees of freedom with stochastic hydrodynamic fields. We have shown that our fluctuating hydrodynamics lipid model yields bilayer dynamics that differ markedly from conventional Langevin dynamics. We have shown that the conservation of momentum and the hydrodynamic transfer of momentum between the lipids plays an important role in producing coherent flows of lipids within the bilayer. In contrast, the Langevin dynamics with a comparable drag greatly suppresses momentum transfer between the lipids and results in only short-range correlations. For diffusion within vesicles, we have shown that our fluctuating hydrodynamics lipid model has interesting spatial correlations that exhibit a vortex-like flow structure. The results show the promise of the methods to capture important hydrodynamic mediated effects previously observed in ex-

PLICIT solvent molecular dynamics simulations and in recent neutron scattering experiments [2, 3, 15]. We expect the SELM fluctuating hydrodynamics methods to provide powerful new approaches for performing investigations of dynamical processes in lipid bilayers utilizing implicit-solvent coarse-grained models.

VI. ACKNOWLEDGEMENTS

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